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Monro-Kellie 2.0: The dynamic vascular and venous pathophysiological components of intracranial pressure

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Abstract

For 200 years, the 'closed box' analogy of intracranial pressure (ICP) has underpinned neurosurgery and neuro-critical care. Cushing conceptualised the Monro-Kellie doctrine stating that a change in blood, brain or CSF volume resulted in reciprocal changes in one or both of the other two. When not possible, attempts to increase a volume further increase ICP. On this doctrine's "truth or relative untruth" depends many of the critical procedures in the surgery of the central nervous system. However, each volume component may not deserve the equal weighting this static concept implies. The slow production of CSF (0.35 ml/min) is dwarfed by the dynamic blood in and outflow (~700 ml/min). Neuro-critical care practice focusing on arterial and ICP regulation has been questioned. Failure of venous efferent flow to precisely match arterial afferent flow will yield immediate and dramatic changes in intracranial blood volume and pressure. Interpreting ICP without interrogating its core drivers may be misleading. Multiple clinical conditions and the cerebral effects of altitude and microgravity relate to imbalances in this dynamic rather than ICP per se. This article reviews the Monro-Kellie doctrine, categorises venous outflow limitation conditions, relates physiological mechanisms to clinical conditions and suggests specific management options.

Keywords

Intracranial pressure, neurotrauma, intracranial hypertension, Monro-Kellie, cerebral venous outflow

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Search strategy and selection criteria

Relevant articles were identified by searches of PubMed (1969 to May 2015), and also from the references they quoted. The search terms 'intracranial pressure', 'intracranial hypertension', 'neurotrauma' and 'traumatic brain injury' were used with others relevant to each section (e.g. 'cervical collar', 'venous drainage').

Introduction

History

Skulls from as far back as 6000 BC show evidence of trephination (thought to be performed to relieve perceived 'pressure' headaches).[1] However, it was in 1783 that a 'science' of intracranial pressure (ICP) was first proposed. Edinburgh physician Alexander Monro[2] (Figure 1(a)), described the skull as a rigid structure containing incompressible brain and stated that the volume of blood must remain constant unless: 'water or other matter is effused or secreted from the blood-vessels' in which case 'a quantity of blood, equal in bulk to the effused matter will be pressed out of the cranium'.

In 1824, Monro's former student George Kellie[3] confirmed that in human and animal autopsies, cerebral (in particular, venous) blood volume was similar no matter what the cause of death (hanging or exsanguination for example). Local pathologist John Abercrombie[4] studied exsanguinated animals and showed that unless the skull and dura were breached,

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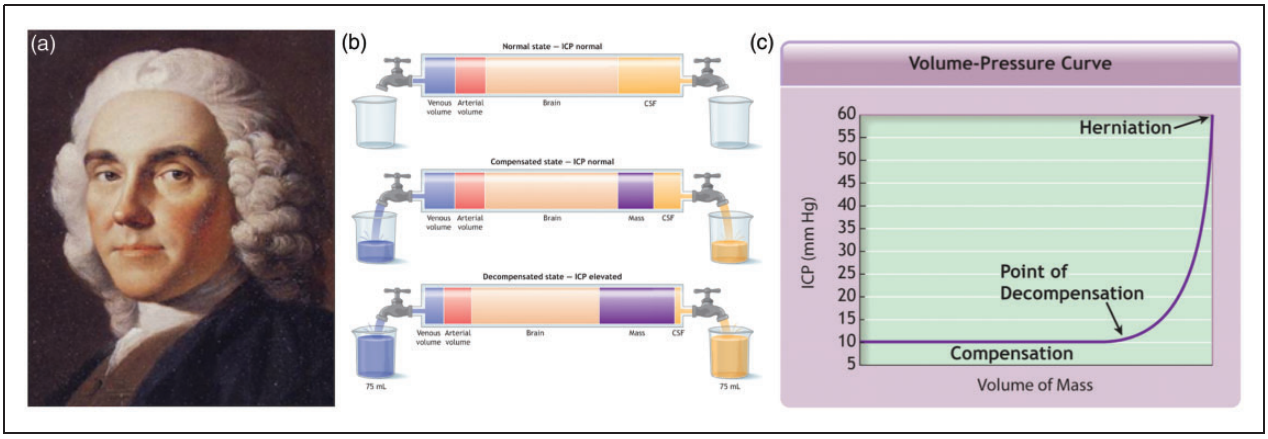

Figure 1. (a) Alexander Monro secundus (1733–1817). Eminent Scottish physician. (b) Adaptation of current explanation of Monro-Kellie doctrine within advanced trauma life support (ATLS) and most critical care teaching demonstrating that additional mass results in a large volume of CSF then venous blood displacement. (c) Demonstrates that once the period of compliance that this displacement affords runs out, there is an exponential rise in pressure. This description fails to explain the importance of volume flow. From ATLS Course Manual 9th edition.

the brain did not exsanguinate in the same way as other organs – the protection the skull offers the brain when ICP is negative to atmospheric pressure often being forgotten. In none of their accounts, however, did any of this Edinburgh group mention cerebral spinal fluid (CSF).

In the 16th century, the peers of Vesalius, a Flemish anatomist, rejected his observation that fluid (rather than gas or spirit) filled the cerebral ventricles. It was the French physiologist François Magendie[5] who firmly established the concept of CSF, demonstrating that fluid communicated between the subarachnoid space and fourth ventricle through the foramen that now bears his name.[5]

Four years later, the English physician George Burrows[6] incorporated the role of CSF into Monro's doctrine, although some were critical, stating that Burrows overplayed CSFs importance and 'magnified it's influence' and role within ICP.[7,8] However, the view that CSF shared blood's importance in ICP regulation was accepted when Harvey Cushing[9] vividly presented the summarised doctrine we know today – that with an intact skull, the sum of the volume of brain, blood and CSF is constant: an increase in one causing a decrease in one or both of the remaining two. Even today, this classic explanation forms the basis of neurosurgery and neurotrauma teaching worldwide (Figure 1(b) and (c)). But a precise understanding of what alters ICP is vital as Weed[10] stated – on this doctrine's 'truth or relative untruth, depend many of the critical procedures in the surgery of the central nervous system'. Interestingly, neuro-critical care practices focusing on arterial and ICP regulation have recently been questioned.[11,12] Normal ICP is ~5–15 mmHg, but is greatly influenced by orthostatic position (for example, it can be negative when standing up) and is generally very similar to cerebral venous pressures (if no distal obstruction).

The dynamic components of ICP

The equal weighting to blood and CSF that the static Monro-Kellie doctrine implies, however, misses the dynamic reality. The slow and (relatively) steady production of CSF (≈0·35 ml/min) is dwarfed by substantial, continuous blood inflow and outflow: at rest, the brain receives approximately 14% of the cardiac output (≈700 ml/min).[13] This is a sizeable volume considering that the average male intracranial volume (including brain and CSF) is only twice this (1473 ml).[14] At any moment in time, the intracranial blood volume is ~100–130 ml (~15% arterial, ~40% venous and ~45% in the microcirculation). CSF volume is ~75 ml (the volume of blood entering in approximately 5 s). Hence, while CSF removal or displacement can reduce ICP, its accumulation is rarely the cause of raised ICP in an acute pathology such as trauma. This is in contrast to CSF obstructive/non-absorption pathology which can result in hydrocephalus and a more gradual rise in ICP.

Arterial influence on ICP. Many have focused on the role of cerebral arterial flow in neuro-critical care. In the early 1970s, Miller and Langfit[15,16] drew attention to the concept of estimated cerebral perfusion pressure (CPP) and its calculation from mean arterial pressure (MAP) and ICP (CPP = MAP – ICP). If this equation was entirely true, ICP would equal MAP-CPP implying no venous involvement. By demonstrating a correlation coefficient of 0.98 between ICP and cortical vein pressure in baboons, Johnston and Rowan[17] suggested that

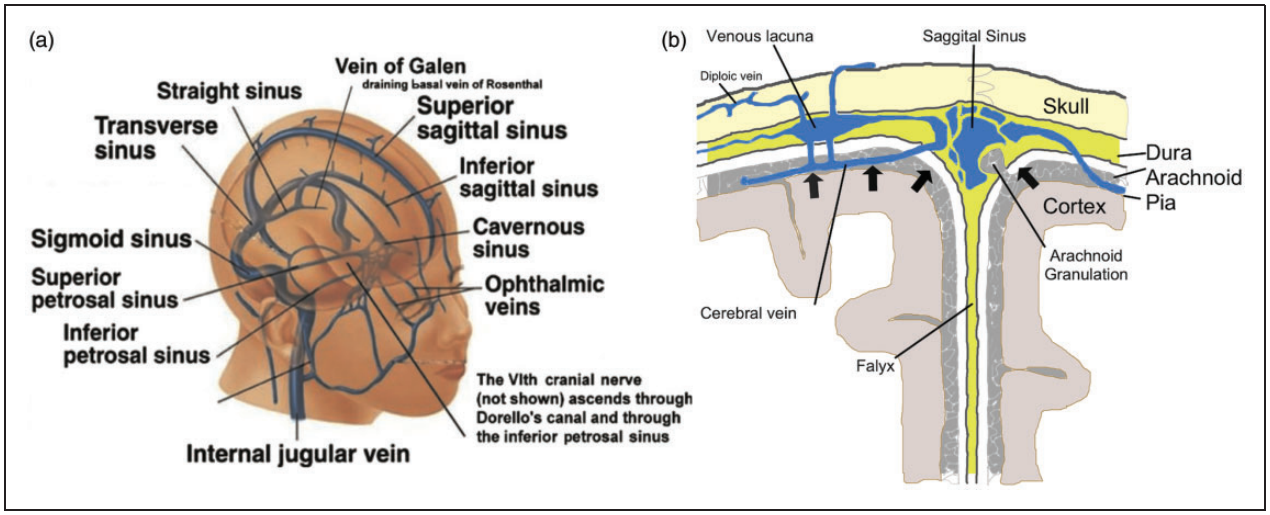

Figure 2. (a) Schematic representation of the commonest pattern of cerebral venous drainage. Adapted from Wilson et al.[24] (b) Cross-sectional representation of the sagittal sinus. The dural reflections create a triangular lumen with no muscular wall in marked contrast to the arterial circulation. This makes venous structures more vulnerable to compression.

the equation was true. However, their studies failed to investigate raised ICP secondary to outflow obstruction. It is well recognised that gentle pressure to the neck over the jugular veins causes an ICP rise. The CPP equation has resulted in diverse guidelines that advocate MAP and CPP targets in the management of brain injury. The European Brain Injury Consortium recommend a MAP of >90 mmHg.[18] The Association of Anaesthetists of Great Britain and Ireland recommend >80 mmHg[19] and The Brain Trauma Foundation advise avoidance of systolic pressures below 90 mmHg.[20] A number of pre-hospital organisations have interpreted this as keeping systolic at 'normal' levels (100 or 120 mmHg[21]). Such targets lack a strong evidence base,[11,22] perhaps in part because a single ideal CPP is unlikely to exist for all the different forms of brain injury and because increasing CPP also tends to increase ICP. Meanwhile, cerebral blood *flow* resulting from any given MAP will differ between individuals (amongst whom the range of 'autoregulation' of flow may vary), and with differences in the vasodilator $PaCO_2$.[23] The 'static' view of the factors regulating ICP, and the focus on arterial inflow alone, has meant that the important influence of cerebral *veins* has been almost entirely neglected.

Venous influence on ICP. The internal jugular veins are fed from three main intra-cerebral venous drainage systems (Figure 2(a)):[24]

1. Cortical veins drain (via bridging veins) into the sagittal sinus which leads posteriorly to the torcula (confluence of sinuses) and then (in most people) to the right transverse sinus.
2. Deeper (anterior) venous drainage occurs into the cavernous sinuses which in turn drain via superior and inferior petrosal sinuses into the jugular bulbs.
3. Central (thalamic) areas drain via a series of small veins into the internal cerebral veins superiorly and the basal veins of Rosenthal inferiorly. These unite (behind the splenium of the corpus callosum) to form the Great Vein of Galen which then drains via the straight sinus into the torcula and then (in most people) to the left transverse sinus.

Cerebral venous drainage is significantly asymmetric in circa 50% of subjects.[25] Transverse sinus drainage is predominantly right sided in approximately 40% of subjects and left sided in about 18%.[26,27] This can usually be demonstrated by a predominately larger sinus on CT or MR venography. Obstruction to a dominant sinus has considerably more effect than obstruction to a non-dominant one. Only a small minority of people have significant drainage through the cervical venous plexi[28] which are of much greater significance in supine mammals such as swine that have not evolved to the gravitational effects of becoming bipeds.[29]

Unlike the strong muscular arterial walls, those of the venous sinuses (being triangular dural reflections (Figure 2(b)) are susceptible to dilatation and compression. In the sitting position, the sagittal sinus has a negative pressure that can result in (potentially fatal) air embolism if opened. When supine, bleeding from the sinuses can be torrential. Likewise, when upright, human internal jugular veins tend to collapse under negative pressure, but engorge on lying.[30]

A role for veins influencing ICP. Concentration on arterial inflow, and failure to consider the role of venous drainage in ICP regulation, means that much important subtlety is missed: reflection suggests that failure for venous efferent flow to precisely match arterial afferent flow (even when the failure results from intracranial venous compromise) will yield immediate and dramatic changes in intracranial volume and pressure. Interpreting the value of regulating ICP, without interrogating its core drivers, may be misleading.

In this regard, much historical work has been forgotten. Leonard Hill[8] demonstrated that venous and CSF pressures were aligned and suggested that, given the lack of valves in the cranio-vertebral venous system, vena caval pressure reflected CSF pressure, and retinal venous distension could reflect intracranial venous pressure. With great insight, he suggested that ICP would be more affected by changes in vascular pressure 'from the venous side to a far greater degree than from the arterial side, because it is on the arterial side that the resistance lies'. Similarly Bedford et al.[31] and Ferris[32] demonstrated the greater importance of the venous system within the Monro-Kellie doctrine. Specifically, increasing central venous pressure (CVP) results in increasing ICP when compliance is lost,[33] and this in turn results in the formation of brain oedema and swelling.[34] Queckenstedt's[35] manoeuvre obstructing venous outflow (which he described in 1916) clearly demonstrates the relationship between increased distal venous pressure and ICP. The velocity of blood in the straight sinus and other venous structures, as measured using transcranial Doppler, has been shown to correlate linearly with ICP.[36]

Since most neurosurgery today is performed under general anaesthesia, we are less aware of which intracranial structures are painful. Ray and Wolff[37] reported multiple observations on up to 30 patient subjects.[37] They demonstrated that pressure on the sinuses (particularly tension at the margins) caused significant headache pain as indicated in Figure 3. Again, the pain of venous structures has largely been forgotten.

Causes of raised cerebral venous pressure

Individual susceptibility to intracranial hypertension may thus be influenced by the anatomical balance of cerebral venous drainage and its compliance. As cerebral blood flow rises, so too must venous drainage. Venous distension will occur up to a limit, after which intravenous pressure (and that upstream, and thus ICP) will rise steeply (in a similar manner to when the limits of compliance are reached in the classic Monro-Kellie doctrine of Figure 1). Anatomical imbalance in venous drainage (i.e. an inability to drain venous blood adequately for a given cerebral blood inflow without raising venous pressures) will predispose to such venous and intracranial hypertension despite what may appear to be an 'atrophic', anatomically compliant system on plain CT. Clinically, this may present with the headache of venous distension when alert or refractory intracranial hypertension if undergoing ICP monitoring. Intracranial venous hypertension can be caused by increased venous resistance/pressures within the cranium or outside it. Within the cranium this can be focal (from outside the sinus, within the sinus wall or within the sinus lumen) or it can be diffuse compression. Further, venous hypertension can originate in the neck, thorax or abdomen. See Table 1 for a suggested classification with clinical examples.

Ia: Focal external venous compression

The thin dural venous sinus walls make them prone to both focal and diffuse compression. Acute compression may result from a depressed skull fracture (Figure 4(a)) or, more commonly, from an expanding mass (e.g. extradural/periosteal haematoma) that may actually be the result of a damaged sinus (Figure 4(b)). Compression may in turn lead to thrombosis and both may cause intracranial hypertension.[38] The location of the fracture and sinus dominance is important in determining the consequence of this. It is our experience that occipital skull fractures over the right transverse sinus are more significant since this is the dominant sinus in most people. Fractures over a hypoplastic sinus rarely have significant effect on ICP.

Glomus tumours can have similar effects, although slow growth allows collateral circulation development and the opening of the opposite transverse sinus and cervical plexus.[39] Epidural abscesses can also restrict venous outflow.[40] Of note, while lesion volume can appear small (see Figure 4(b)), the impact on ICP may be wholly unrelated and excessive (compared to the apparent reserve space/compliance of a CT image).

Treatment depends on how significant the resulting venous compromise is. A conservative management with permissive intracranial hypertension may suffice, although elevating a fracture (Figure 4(a)) or a single burr hole can reduce the mass compressing the sinus and subsequent intracranial hypertension.

Ib: Focal venous sinus stenosis

Focal transverse sinus stenosis (graded as shown in Figure 4(c))[41] is associated with idiopathic intracranial hypertension (IIH characterised by headache, loss of peripheral vision and nausea).[42,43] Bilateral stenosis is found in up to 90% of sufferers.[44–46] Moreover, endoluminal stenting of stenotic regions can dramatically improve symptoms.[45,47–49] IIH tends to be a disease

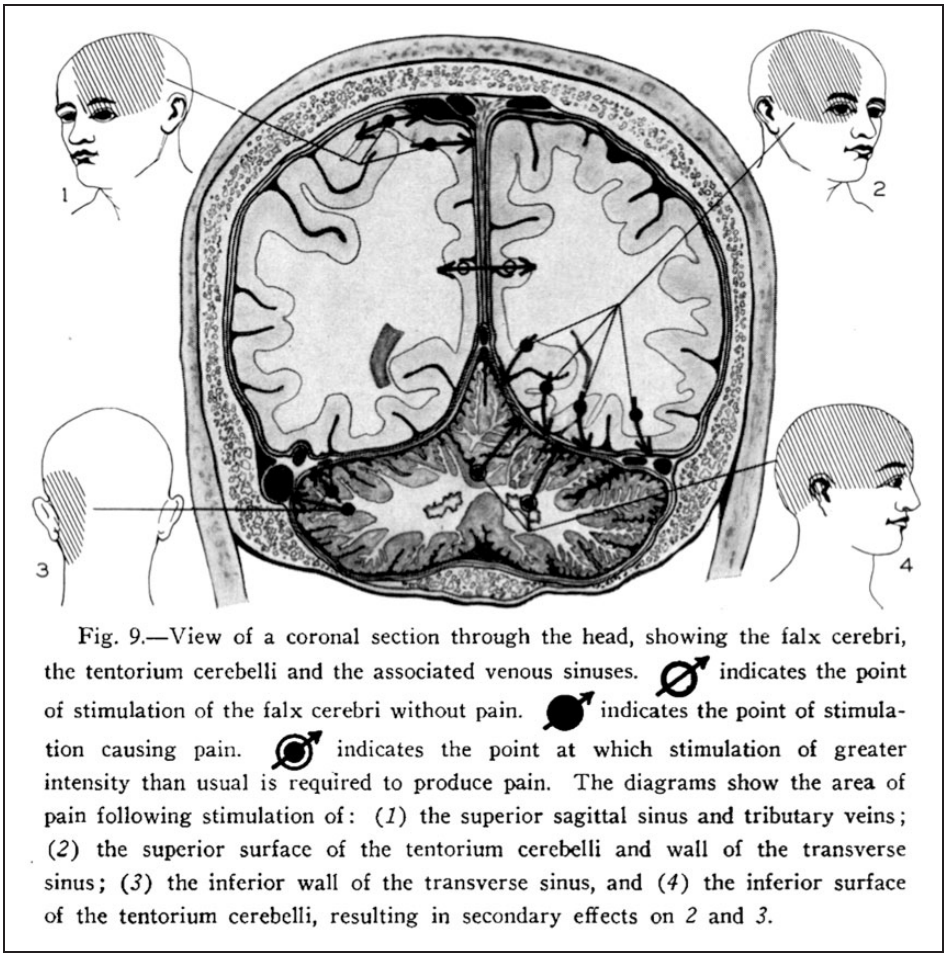

Fig. 9.—View of a coronal section through the head, showing the falx cerebri, the tentorium cerebelli and the associated venous sinuses. indicates the point of stimulation of the falx cerebri without pain. indicates the point of stimulation causing pain. indicates the point at which stimulation of greater intensity than usual is required to produce pain. The diagrams show the area of pain following stimulation of: (*1*) the superior sagittal sinus and tributary veins; (*2*) the superior surface of the tentorium cerebelli and wall of the transverse sinus; (*3*) the inferior wall of the transverse sinus, and (*4*) the inferior surface of the tentorium cerebelli, resulting in secondary effects on *2* and *3*.

Figure 3. View of a coronal section through the head, showing the falx cerebri, the tentorium cerebelli, and the associated venous sinuses. The full legend is within the figure.[37]

of young overweight women. The additional weight may be contributory to intra-cerebral venous hypertension (through mechanisms III, IV, and V outlined below), tipping a patient that would otherwise be asymptomatic into the decompensated category.

Ic: Focal internal obstruction

Ecker[50] described dural sinus thrombosis associated with skull fracture and many more cases have been reported.[51–66] Nonetheless, it is considered rare – perhaps due to lack of systematic approaches to identify its presence. Indeed, in a series of 21 ventilated head injury patients with a skull fracture over the sinus, Kolias et al.[67] found that sinus thrombosis was common (affecting 8 (=38%) patients) and associated with a high mortality (3 of the 8 died compared to none of the 13 without thrombosis). This group also have impaired pressure reactivity. A recent study by our group has demonstrated that 48% of patients with occipital skull fractures over the transverse sinus had thrombosis and a further 13% had external obstruction (see above) sometimes with thrombosis (n = 29).[69]

Treatments have included conservative management,[59] acetazolamide, anticoagulation,[52] ventricular-peritoneal (VP) shunt insertion,[53] endovascular treatment[58] and decompressive craniectomy (DC).[56] Conservative management is reasonable in the absence of progressive symptoms. In symptomatic cases where there is a depressed skull fracture over the sinus, elevation (raising of the depressed bone piece) should be considered if there is flow disruption or symptomatic thrombosis. This can safely be achieved by drilling off just the bone that is holding the fragment depressed and allowing it to rise (Figure 4(a)). Ozer et al.[62] reported elevating 17 depressed skull fractures over sinuses.[62] While they make no mention of sinus thrombosis, they reported 'massive blood loss' in 11 of the cases although control was regained. Two of the patients died from associated intra-cerebral lesions. If the thrombosis is progressing and results from an undisplaced fracture then endovascular treatment where

Table 1. Suggested classification of venous causes of intracranial hypertension.

		Classification	Location of resistance/pressure	Clinical examples
I	a	Focal extramural venous sinus compression	External compression of a significant venous sinus at a focal point	Depressed skull fracture, periosteal hematoma, tumor.
	b	Focal intermural venous sinus stenosis	A focal narrowing within the sinus wall	Idiopathic intracranial hypertension
	c	Focal intramural venous sinus obstruction	Obstruction within a significant venous sinus	Sagittal or transverse sinus thrombosis.
	d	Diffuse venous compression	Throughout the venous tree	Any cause of cerebral swelling e.g. hypoxia, cerebral edema, contusions
II		Extracranial venous hypertension – cervical	Within the neck	Cervical collars, hanging
III		Extracranial venous hypertension – thoracic	Within the thorax	Any cause of increased intra-thoracic pressure – Chest infection, adult respiratory distress syndrome, mechanical ventilation
IV		Extracranial venous hypertension – abdominal	Within the abdomen	Any cause of increased abdominal pressure - obesity, obstruction
V		Orthostatic/gravity		Visual impairment and raised ICP/space obstruction syndrome

available may be considered. Failure to elevate depressed skull fractures over the sagittal sinus can result in IIH.[63–65,70]

Id: Diffuse compression of the venous system

Diffuse brain swelling can also cause generalised venous compression creating an internal starling type resistor. Recent evidence implies that in many cases of IIH, the entire dural sinus tree appears to be compressed.[71] A cycle of venous hypertension, cerebral swelling, further venous compression and therefore hypertension occurs. This cycle can be broken with CSF drainage although it is likely to recur again, not as CSF accumulates but as venous hypertension recurs. Pickard et al.[46] studied CSF and sagittal sinus pressures in nine patients with IIH. During CSF, drainage CSF pressure decreased below central venous pressure (CVP), while the sagittal sinus pressure fell only to CVP and not lower. This suggests that functional obstruction of venous outflow through the dural sinuses is present in many IIH cases. Raised CSF pressure partly obstructs venous sinus outflow, thereby increasing sinus pressure and then CSF pressure, et sequor.

It is our experience that a similar phenomenon can occur with other causes of cerebral swelling, such as that resulting from trauma. Figure 5 is a CT venogram of a patient with diffuse cerebral swelling following trauma which also demonstrates diffuse compression of both transverse sinuses. A DC was performed for refractory high ICP. A post-operative CT venogram demonstrated marked increase in sinus calibre.

The diffuse parenchymal volume increase that occurs with prolonged hypoxia (such as occurs at altitude) has recently also been demonstrated to cause venous compression which may in turn raise ICP (Sagoo et al, 2016).

Venous pressures can be inferred from brain CT scans. The superior ophthalmic vein is normally between 1.4 and 3.6 mm (mean 2.2 mm).[72] Bilateral superior ophthalmic vein enlargement (considered > 2–3 mm) is associated with diffuse cerebral swelling as reported in 11 cases.[73]

Extracranial causes of cerebral venous hypertension

II Cervical. Neck pressure is well recognised to have a significant effect on ICP. Queckenstedt's[35] test is now an outdated technique for investigating spinal stenosis. The test comprised jugular venous compression with concurrent lumbar puncture. Those with spinal stenosis have a slower lumbar pressure CSF rise than those without. The author has modified this technique. By applying pressure over each jugular (separately) while watching invasively monitored ICP, a crude assessment can be made as to the dominance of venous drainage and the degree of venous compliance.

Poor head position is often overlooked but is an incredibly important cause of raised ICP. Mavrocordatos et al.[74] in a study of elective neurosurgery patients without raised ICP (n = 15) demonstrated that ICP was lowest with the head in a neutral position. Flexion and worse still flexion with rotation caused significant increases in ICP (e.g. from mean 8.8 mmHg

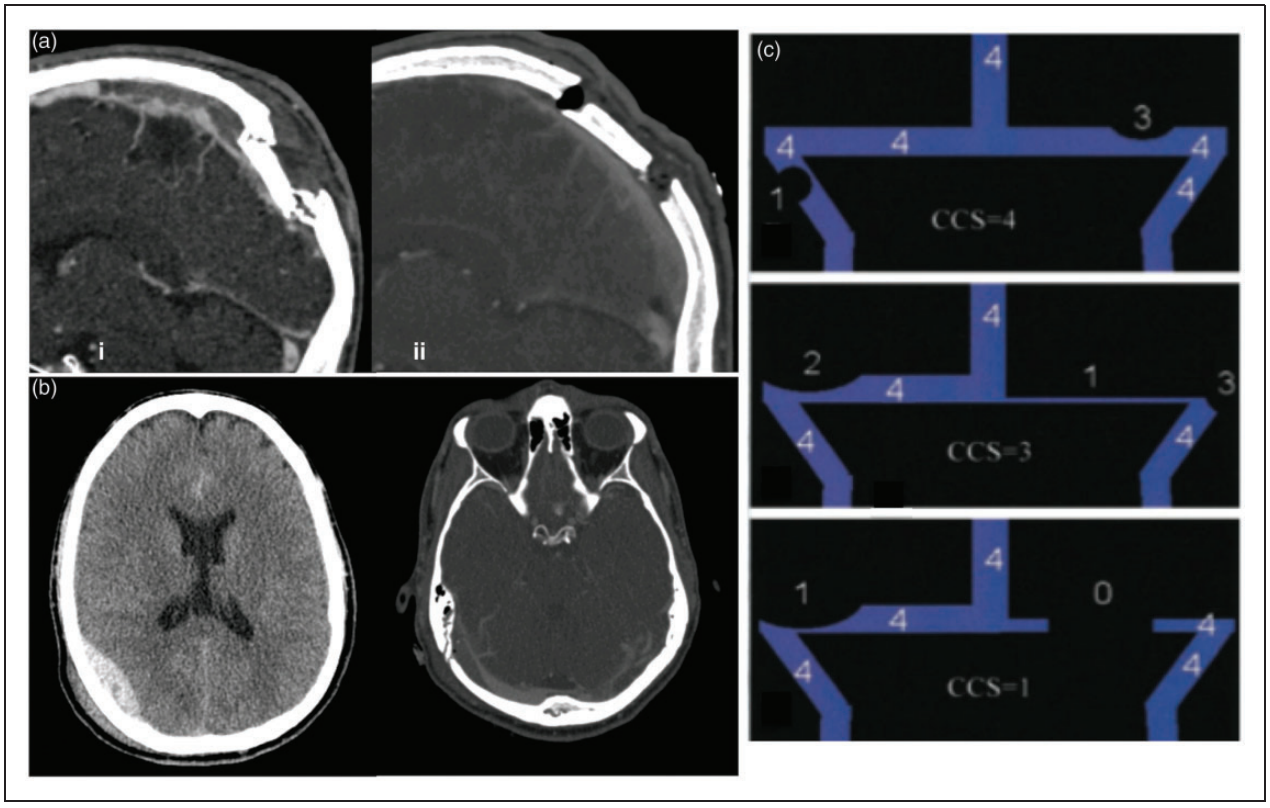

Figure 4. (a) Depressed skull fracture and subsequent (superior sagittal sinus) SSS thrombosis caused by a hammer blow – (i) midsagittal reconstruction on day 2 with increasing headaches demonstrating SSS thrombosis, (ii) – midsagittal reconstruction of CTV day 2 post op demonstrating resolution of SSS thrombosis. (b) Occipital extradural from fracture overlying the right transverse sinus. (i) plain axial CT scan, (ii) CT Venogram. The extradural can be seen compressing and narrowing the dominant right transverse sinus. Note the relatively hypoplastic left transverse sinus. (c) The combined conduit score (CCS) adapted from Farb et al.[41] Each transverse sinus is assessed separately and the area with the greatest stenosis graded (0–4) in relation to the superior sagittal sinus (SSS). 0 = discontinuity/aplastic segment; 1 = hypoplasia/severe stenosis with cross-sectional diameter less than 25% of the SSS; 2 = moderate stenosis (25–50% of SSS cross-sectional area); 3 = mild stenosis (50–75% of SSS cross-sectional area), and 4 = no significant stenosis (75–100% of SSS cross-sectional area). Both left and right scores are summed to give a total CCS.

when neutral to 16.2 mmHg when rotated to the right and flexed). This is an even greater problem in children with larger occiputs (resulting in flexion) and floppier necks.[75]

Cervical collars can increase ICP from about 4.5 mmHg[76–78] to as much as 14.5 mmHg,[77] the rise being greater in those with baseline ICP > 15 mmHg.[78] This probably reflects the degree of intracranial compliance: a patient who can accommodate less cerebral venous engorgement will have a more immediate rise in ICP. These mean pressure increases may be small, but they can have profound effects if sustained[79] or if the patient is at the limit of their compliance. Stone et al.[80] have recently demonstrated that collar application causes an increase in internal jugular vein cross-sectional area of 37% (95% confidence interval [CI] = 20% to 53%) strongly supporting the hypothesis that it is venous compression and resulting congestion that underlies the collar induced ICP increase. As a result, the benefits of cervical collars in the acute management of traumatic brain injury are questionable to say the least.[81]

Other cervical causes of acute venous hypertension include near hanging and strangulation which can induce venous/haemorrhagic infarction.[82] More chronic causes include jugular syndromes blocking outflow[83] and superior vena cava obstruction.[84] A degree of internal jugular stenosis may also occur in patients with IIH.[85]

III: Intra-thoracic. Positive pressure ventilation in the treatment of chest infection and Adult Respiratory Distress syndrome (ARDS) can severely raise intra-thoracic pressure as can the application of positive end expiratory pressure (PEEP) with inter-individual variation in ICP possibly reflecting differences in venous compliance – i.e. whether venous drainage is still adequate.[86,87] Intra-thoracic pressure regulator

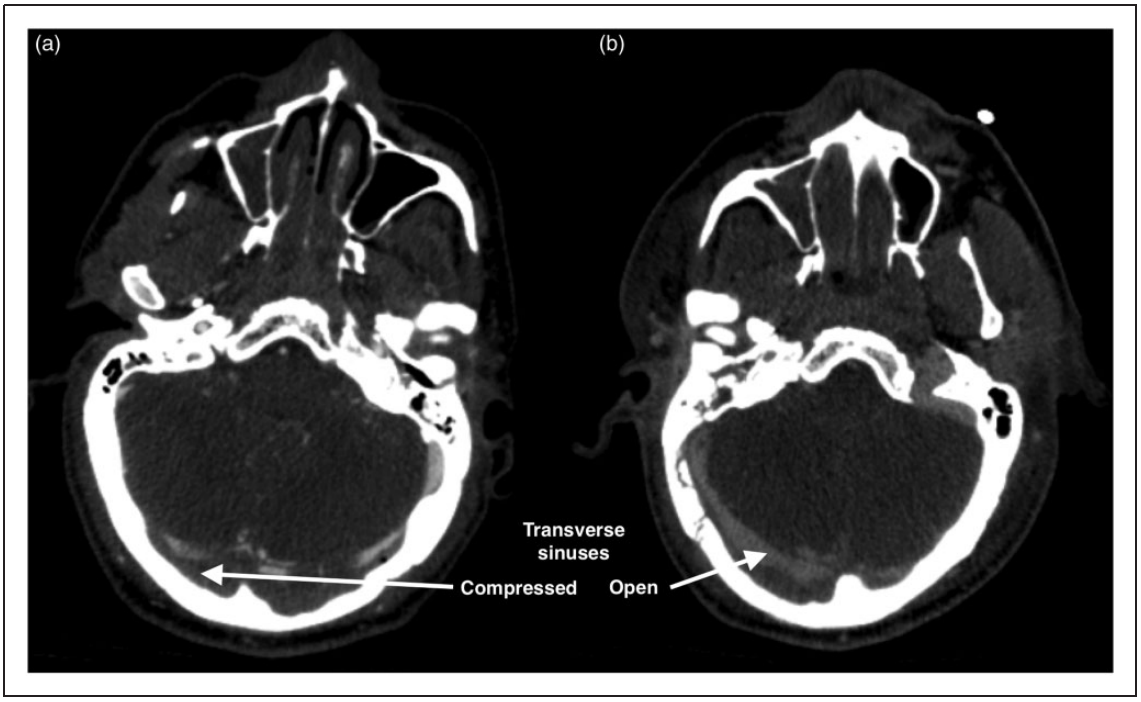

Figure 5. CT venograms of a male patient aged 48-year-old male with refractory intracranial hypertension. (a) Transverse sinuses severely effaced with raised intracranial pressure. (b) Following bifrontal decompressive craniectomy the transverse sinus calibre increases dramatically.

use (which apply negative pressure during the expiratory phase of ventilation with the aim of reducing intra-thoracic pressure, enhancing venous return, and increasing cardiac output) may reduce ICP.[88]

IV: Intra-abdominal. Abdominal compartment syndrome (raised intra-abdominal pressure causing organ dysfunction) raises ICP in brain-injured patients[89] which can be reduced by decompressive laparotomy (DL).[90] Of 24 patients who underwent both DC and DL for refractory ICP,[90] 15 underwent DC before DL and 9 underwent DL before DC. While both DL and DC significantly reduced ICP, DL, not surprisingly, also reduced intra-thoracic pressure.[90] Results of DL are comparable to DC with 17 out of 17 patients (without abdominal compartment syndrome) benefiting from a reduction (mean 27.5 mmHg to 17.5 mmHg) in otherwise refractory ICP, although in six (all of whom subsequently died) this fall was transient.[91]

Scalea et al.'s[92] team point out that fluid therapy to raise CPP may also cause retroperitoneal and visceral oedema increasing intra-abdominal pressure and interstitial pulmonary oedema (also increasing intra-thoracic pressures). It has also been suggested that the raised intra-abdominal pressures in preeclampsia cause raised cerebral venous and ICPs and contribute to the intracerebral haemorrhage that is sometimes seen.[92]

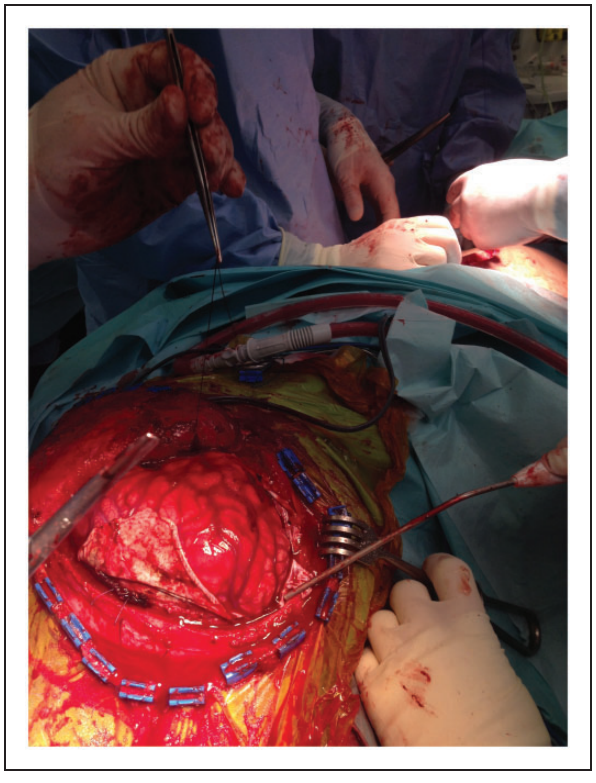

Figure 6. Brain herniation occurring at the time of abdominal closure (see text)[93].

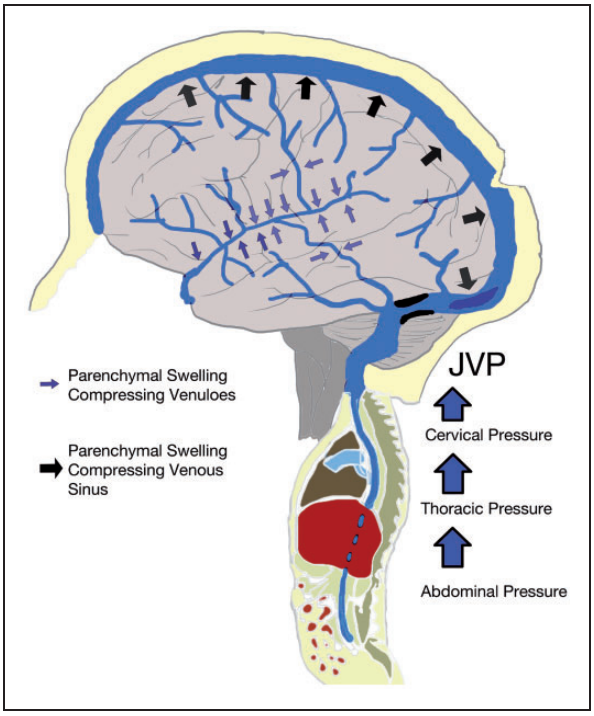

Figure 7. Diagram demonstrating that relative venous outflow restriction can occur intracranially (with compression/obstruction (e.g. with thrombus or fractures) of isolated or diffuse venous structures) and extracranially (from cervical, thoracic and abdominal pressures).

Table 2. Treatment options to minimise the venous contribution of intracranial hypertension.

Venous cause of intracranial hypertension	Treatment
Orthostatic/ hydrostatic	Avoid hypoxia. Elevate head. Avoid abdominal compression. If intubated, non-depolarising paralysis.
Cervical	Avoid neck vein compression (e.g. with collars) and maintain in neutral position or position where dominant jugular is optimised. Avoid "double chin" which compresses jugular.
Intracranial causes	Looks for dominance in transverse sinus drainage. Relieve direct sinus compression, e.g. by depressed skull fracture elevation, release of clot compressing sinus. For sinus thrombosis consider anticoagulation or interventional radiological management. Consider decompressive craniectomy.
Thoracic causes	Relieve causes of increased intra-thoracic pressure. Minimise risk of infection/ARDS. Ventilate with no excessive positive pressure.
Abdominal causes	Relieve causes of intra-abdominal hypertension. Treat constipation. Place urinary catheter. In extreme circumstances, consider decompressive laparotomy.

Note: The order reflects the clinical order in which they are usually managed.

Figure 6 demonstrates brain herniation occurring as an abdominal wound is closed. This patient who had an acute subdural removed concurrently with a splenectomy for trauma developed acute bleeding from his right transverse sinus and brain herniation as the abdomen was closed, reflecting the rise in venous pressure.[93]

V: Hydrostatic/gravity–related cerebral venous hypertension. Microgravity: In recent years a very significant number of astronauts have complained of loss of peripheral vision (so-called visual impairment-ICP),[94] a symptom also occurring in IIH. The lack of gravity results in upper thoracic venous hypertension and hence a similar pathological process may underlie this condition.[24] This phenomenon has become a considerable problem, jeopardising human exploration to Mars until resolved.

Vasomotor tone: The administration of non-depolarising paralytic agents in intensive care can reduce ICP, while depolarising relaxants cause a transitory ICP rise.[95] Both effects likely result from transmission of muscle tension through the venous system.

Hypoxia and conditions increasing CBF: Conditions that result in increased arterial inflow may 'bring out'/decompensate venous hypertension in those with little reserve. Hypobaric hypoxia increases cerebral blood flow to maintain brain oxygenation[96,97] and limitations in cerebral venous drainage may underlie the pathogenesis of high-altitude headache through cerebral venous engorgement.[98] Recent work by Sagoo et al.[99] have demonstrated that venous outflow restriction appears to have a contributory role in the pathogenesis of cerebral oedema.

There is increasing interest regarding the possible (and controversial) involvement of the venous system in other neurological conditions such as multiple sclerosis,[100] normal pressure hydrocephalus,[101] dementia[102] and leukoaraiosis.[103] Chronic cerebrospinal venous insufficiency and decreased venous vasculature appear to be a feature of MS, but the relationship between causation and association is not clear.[104] The recent discovery of the co-location of lymphatic vessels with dural sinuses may be of relevance but further investigation is needed.[105]

Summary

While the traditional Monroe-Kellie doctrine holds, imbalances in arterial inflow and venous outflow also affect ICP. The venous outflow can be altered intracranially and extracranially (Figure 7). Table 2 demonstrates venous causes of intracranial hypertension and outlines treatment options.

Conclusion

The balance between cerebral blood in and outflow is vital in maintaining normal ICP. Restrictions in outflow can be as, if not more, significant than mass accumulation within the cranium. There has been a concentration of interest in CPP and ICP; however, the considerable importance of the venous side has often been overlooked. ICP is a function of venous outflow, a combination of intra-cerebral resistance and cervical, thoracic and abdominal pressures. If there was no resistance to venous outflow ICP would be zero, hence using intravenous fluids to 'maintain CPP' may increase CVP and worsen ICP (and ironically CPP). The dynamic influence of blood flow on ICP is an essential component of the Monro-Kellie doctrine.

There is increasing evidence that venous pathology is central to multiple conditions that cause a rise in ICP. A greater understanding and appreciation of the role of the venous system in neuro-critical care is vital.

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Author contributions

MW authored this manuscript. The concepts were developed based on his work as a neurosurgeon, pre-hospital care physician and high-altitude research with many years working with the people listed in the Acknowledgements section.

References

1. Restak R. *Fixing the brain. Mysteries of the mind*. Washington, DC: National Geographic Society, 2000.
2. Monro A. *Observations on the structure and function of the nervous system*. Edinburgh: Creech and Johnson, 1783.
3. Kellie G. An account of the appearances observed in the dissection of two of the three individuals presumed to have perished in the storm of the 3rd, and whose bodies were discovered in the vicinity of Leith on the morning of the 4th November 1821 with some reflections on the pathology of the brain. *Transac Medico Chirurg Soc Edinburgh* 1824; 1: 84–169.
4. Clarke C and Abercrombie J. *Pathological and practical researches in disease of the brain and spinal cord*. Edinburgh: Carey, Lea and Blanchard, 1928.
5. Magendie F. *Recherches anatomique et physiologique sur le liquide céphalo-rachidien ou cérebro-spinal*. Paris: Méquignon-Marvis fils, 1842.
6. Burrows G. *On disorders of the cerebral circulation and on the connection between affections of the brain and diseases of the heart*. Philadelphia: Lea and Blanchard, 1848.
7. Reid J. Burrows on cerebral circulation. *Edinburgh Mon J Med Sci* 1846; 111–123.
8. Hill L. *The physiology and pathology of the cerebral circulation*. London: J&A Churchill, 1896.
9. Cushing H. *The third circulation in studies in intracranial physiology and surgery*. London: Oxford University Press, 1926.
10. Weed LH. Some limitations on the Monro-Kellie hypothesis. *Arch Surg* 1929; 18: 1049.
11. Kirkman MA and Smith M. Intracranial pressure monitoring, cerebral perfusion pressure estimation, and ICP/CPP-guided therapy: a standard of care or optional extra after brain injury? *Br J Anaesth* 2014; 112: 35–46.
12. Chesnut RM, Temkin N, Carney N, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. *N Engl J Med* 2012; 367: 2471–2481.
13. McArdle WD, Katch FI and Katch VL. *Exercise physiology*, 7th ed. Baltimore: Lippincott, Williams & Wilkins, 2006.
14. Abbott AH, Netherway DJ, Niemann DB, et al. CT-determined intracranial volume for a normal population. *J Craniofac Surg* 2000; 11: 211–223.
15. Miller JD, Stanek AE and Langfitt TW. A comparison of autoregulation to changes in intracranial and arterial pressure in the same preparation. *Eur Neurol* 1970; 6: 34–38.
16. Miller JD, Stanek A and Langfitt TW. Concepts of cerebral perfusion pressure and vascular compression during intracranial hypertension. *Prog Brain Res* 1971; 35: 411–432.
17. Johnston IH and Rowan JO. Raised intracranial pressure and cerebral blood flow. 3. Venous outflow tract pressures and vascular resistances in experimental intracranial hypertension. *J Neurol Neurosurg Psychiatry* 1974; 37: 392–402.

18. Maas AIA, Dearden MM, Teasdale GMG, et al. EBIC-guidelines for management of severe head injury in adults. *Acta Neurochir (Wien)* 1997; 139: 286–294.
19. Recommendations for the safe transfer of patients with brain injury. London, 2006, www.aagbi.org/sites/default/files/braininjury.pdf. (accessed 23 April 2016).
20. Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, et al. Guidelines for the management of severe traumatic brain injury. I. Blood pressure and oxygenation. *J Neurotrauma* 2008; 25: 276–278.
21. South Western Ambulance Service. swast.nhs.uk. 2013, www.swast.nhs.uk/Downloads/Clinical%20Guidelines%20SWASFT%20staff/CG12_Head_Injury.pdf (8 accessed June 2014).
22. Harris TT, Thomas GORG and Brohi KK. Early fluid resuscitation in severe trauma. *BMJ* 2012; 345: e5752–e5752.
23. Coles JPJ, Minhas PS, Fryer TD, et al. Effect of hyperventilation on cerebral blood flow in traumatic head injury: clinical relevance and monitoring correlates. *Crit Care Med* 2002; 30: 1950–1959.
24. Wilson MH, Imray CHE and Hargens AR. The headache of high altitude and microgravity–similarities with clinical syndromes of cerebral venous hypertension. *High Alt Med Biol* 2011; 12: 379–386.
25. Beards SCS, Yule SS, Kassner AA, et al. Anatomical variation of cerebral venous drainage: the theoretical effect on jugular bulb blood samples. *Anaesthesia* 1998; 53: 627–633.
26. Boushel R, Durgun BB, Ilglt ETE, et al. Evaluation by angiography of the lateral dominance of the drainage of the dural venous sinuses. *Surg Radiol Anat* 1993; 15: 125–130.
27. Singh M, Nagashima M and Inoue Y. Anatomical variations of occipital bone impressions for dural venous sinuses around the torcular Herophili, with special reference to the consideration of clinical significance. *Surg Radiol Anat* 2004; 26: 480–487.
28. Doepp F, Schreiber SJ, Munster TV, et al. How does the blood leave the brain? A systematic ultrasound analysis of cerebral venous drainage patterns. *Neuroradiology* 2004; 46: 565–570.
29. Lavoie P, Metellus P, Velly L, et al. Functional cerebral venous outflow in swine and baboon: feasibility of an intracranial venous hypertension model. *J Invest Surg* 2008; 21: 323–329.
30. Gisolf J, Van Lieshout JJ, van Heusden K, et al. Human cerebral venous outflow pathway depends on posture and central venous pressure. *J Physiol* 2004; 560: 317–327.
31. Bedford THB, Burgess KR, Johnson P, et al. The effect of increased intracranial venous pressure on the pressure of the cerberospinal fluid. *Brain* 1935; 58: 429–447.
32. Ferris EB. The effect of high intracranial venous pressure upon the cerebral circulation and its relation to cerebral symptoms. *J Clin Invest* 1939; 18: 19–24.
33. Raisis JE, Kindt GW, McGillicuddy JE, et al. The effects of primary elevation of cerebral venous pressure on cerebral hemodynamics and intracranial pressure. *J Surg Res* 1979; 26: 101–107.
34. Cuypers J, Cuypers J, Matakas F, et al. Effect of central venous pressure on brain tissue pressure and brain volume. *J Neurosurg* 1976; 45: 89–94.
35. Queckenstedt H. Diagnose der Ruckenmark-kompression. *Deut Nervenheilkd* 1916; 55: 325.
36. Schoser BG, Riemenschneider N and Hansen HC. The impact of raised intracranial pressure on cerebral venous hemodynamics: a prospective venous transcranial Doppler ultrasonography study. *J Neurosurg* 1999; 91: 744–749.
37. Ray BS and Wolff HG. Experimental studies on headache: pain-sensitive structures of the head and their significance in headache. *Arch Surg* 1940; 4: 813–856.
38. Maurice-Williams RSR, DeLong WB and Burney RE. Lateral sinus compression from an epidural hematoma: report of a patient with delayed neurological deterioration. *Mil Med* 1969; 134: 521–524.
39. Goldsmith P, Burn DJ, Coulthard AA, et al. Extrinsic cerebral venous sinus obstruction resulting in intracranial hypertension. *Postgrad Med J* 1999; 75: 550–551.
40. Ludemann JP, Poskitt K and Singhal A. Intracranial hypertension secondary to sigmoid sinus compression by group a streptococcal epidural abscess. *J Laryngol Otol* 2010; 124: 93–95.
41. Farb RI, Vanek I, Scott JN, et al. Idiopathic intracranial hypertension: the prevalence and morphology of sinovenous stenosis. *Neurology* 2003; 60: 1418–1424.
42. Binder DK, Horton JC, Lawton MT, et al. Idiopathic intracranial hypertension. *Neurosurgery* 2004; 54: 538–51; discussion 551–552.
43. Ball AK and Clarke CE. Idiopathic intracranial hypertension. *Lancet Neurol* 2006; 5: 433–442.
44. Bono F, Giliberto C, Mastrandrea C, et al. Transverse sinus stenoses persist after normalization of the CSF pressure in IIH. *Neurology* 2005; 65: 1090–1093.
45. Higgins JNP, Cousins C, Owler BK, et al. Idiopathic intracranial hypertension: 12 cases treated by venous sinus stenting. *J Neurol Neurosurg Psychiatry* 2003; 74: 1662–1666.
46. Pickard JD, Czosnyka Z, Czosnyka M, et al. Coupling of sagittal sinus pressure and cerebrospinal fluid pressure in idiopathic intracranial hypertension – a preliminary report. *Acta Neurochir Suppl* 2008; 102: 283–285.
47. Donnet A, Metellus P, Levrier O, et al. Endovascular treatment of idiopathic intracranial hypertension: clinical and radiologic outcome of 10 consecutive patients. *Neurology* 2008; 70: 641–647.
48. Higgins J, Owler BK, Cousins C, et al. Venous sinus stenting for refractory benign intracranial hypertension. *Lancet* 2002; 359: 228–230.
49. Owler BK, Parker G, Halmagyi GM, et al. Cranial venous outflow obstruction and pseudotumor cerebri syndrome. *Adv Tech Stand Neurosurg* 2005; 30: 107–174.
50. Ecker AD. Linear fracture of the skull across the venous sinuses. *N Y State J Med* 1946; 46: 1120.

51. Kumar GSSG, Chacko AGA and Chacko MM. Superior sagittal sinus and torcula thrombosis in minor head injury. *Neurol India* 2004; 52: 123–124.
52. Dalgiç AA, Seçer MM, Ergüngör FF, et al. Dural sinus thrombosis following head injury: report of two cases and review of the literature. *Turk Neurosurg* 2008; 18: 70–77.
53. Forbes JA, Reig AS, Tomycz LD, et al. Intracranial hypertension caused by a depressed skull fracture resulting in superior sagittal sinus thrombosis in a pediatric patient: treatment with ventriculoperitoneal shunt insertion. *J Neurosurg Pediatr* 2010; 6: 23–28.
54. Kabataş SS, Civelek EE, Sencer AA, et al. [A case of superior sagittal sinus thrombosis after closed head injury]. *Ulus Travma Acil Cerrahi Derg* 2004; 10: 208–211.
55. Kobayashi S, Hongo K, Koyama T, et al. Re-occlusion of the superior sagittal sinus after surgical recanalisation. *J Clin Neurosci* 2004; 11: 322–324.
56. Barbati G, Montà G, Coletta R, et al. Post-traumatic superior sagittal sinus thrombosis. Case report and analysis of the international literature. *Minerva Anestesiol* 2003; 69: 919–925.
57. Ferrera PC. Sagittal sinus thrombosis after closed head injury. *Am J Emerg Med* 1998; 16: 4–4.
58. Kuether TA, O'Neill O, Nesbit GM, et al. Endovascular treatment of traumatic dural sinus thrombosis: case report. *Neurosurgery* 1998; 42: 1163–1166; discussion 1166–1167.
59. Satoh HH, Uozumi TT, Kiya KK, et al. [Venous thrombosis after closed head injury: a report of two cases presenting as intracranial hypertension]. *No Shinkei Geka* 1993; 21: 953–957.
60. Hesselbrock RR, Theis MK, Sawaya RR, et al. Superior sagittal sinus thrombosis after closed head injury. *Neurosurgery* 1985; 16: 825–828.
61. Plessis du JJ. Depressed skull fracture involving the superior sagittal sinus as a cause of persistent raised intracranial pressure: a case report. *J Trauma* 1993; 34: 290–292.
62. Ozer FD, Yurt A, Sucu HK, et al. Depressed fractures over cranial venous sinus. *J Emerg Med* 2005; 29: 137–139.
63. Yokota H, Eguchi T, Nobayashi M, et al. Persistent intracranial hypertension caused by superior sagittal sinus stenosis following depressed skull fracture. Case report and review of the literature. *J Neurosurg* 2006; 104: 849–852.
64. Vender JR and Bierbrauer K. Delayed intracranial hypertension and cerebellar tonsillar necrosis associated with a depressed occipital skull fracture compressing the superior sagittal sinus. Case report. *J Neurosurg* 2005; 103: 458–461.
65. Fuentes SS, Bärtsch P, Metellus PP, et al. Depressed skull fracture overlying the superior sagittal sinus causing benign intracranial hypertension. Description of two cases and review of the literature. *Br J Neurosurg* 2005; 19: 438–442.
66. Donovan DJD. Simple depressed skull fracture causing sagittal sinus stenosis and increased intracranial pressure: case report and review of the literature. *Surg Neurol* 2005; 63: 4–4.
67. Kolias AG, Higgins JN, Scoffings DJ, et al. Skull fractures in patients with traumatic brain injury: when to consider CT venography? *Brit J Neurosurg* 2012; 26: 132–174.
68. Kolias AG, Czosnyka M, Smielewski P, et al. Post-traumatic venous outflow obstruction: the effects on intracranial pressure, cerebrovascular pressure reactivity and outcome. w3.cns.org. 2012, http://w3.cns.org/dp/2012CNS/1394.pdf (accessed 4 October 2012).
69. Hendrickson S, Murahari S, Scotter J, et al. Venous sinus injuries are common with occipital skull fractures. *Scand J Trauma Resusc Emerg Med* 2014; 22: O8.
70. Uzan M, Ciplak N, Dashti SG, et al. Depressed skull fracture overlying the superior sagittal sinus as a cause of benign intracranial hypertension. Case report. *J Neurosurg* 1998; 88: 598–600.
71. Rohr A, Bindeballe J, Riedel C, et al. The entire dural sinus tree is compressed in patients with idiopathic intracranial hypertension: a longitudinal, volumetric magnetic resonance imaging study. *Neuroradiology* 2012; 54: 25–33.
72. Brightbill TC, Martin SB and Bracer R. The diagnostic significance of large superior ophthalmic veins in patients with normal and increased intracranial pressure: CT and MR evaluation. *Neuro Ophthal* 2001; 26: 93–101.
73. Khanna RK, Pham CJ, Malik GM, et al. Bilateral superior ophthalmic vein enlargement associated with diffuse cerebral swelling. Report of 11 cases. *J Neurosurg* 1997; 86: 893–897.
74. Mavrocordatos P, Bissonnette B and Ravussin P. Effects of neck position and head elevation on intracranial pressure in anaesthetized neurosurgical patients: preliminary results. *J Neurosurg Anesthesiol* 2000; 12: 10–14.
75. Goldberg RN, Joshi A, Moscoso P, et al. The effect of head position on intracranial pressure in the neonate. *Crit Care Med* 1983; 11: 428–430.
76. Mobbs RJ, Vuyk J, Van Den Bos J, et al. Effect of cervical hard collar on intracranial pressure after head injury. *ANZ J Surg* 2002; 72: 389–391.
77. Davies G, Deakin C and Wilson A. The effect of a rigid collar on intracranial pressure. *Injury* 1996; 27: 647–649.
78. Hunt K, Hallworth S and Smith M. The effects of rigid collar placement on intracranial and cerebral perfusion pressures. *Anaesthesia* 2001; 56: 511–513.
79. Craig GR and Nielsen MS. Rigid cervical collars and intracranial pressure. *Intensive Care Med* 1991; 17: 504–505.
80. Stone MB, Tubridy CM and Curran R. The effect of rigid cervical collars on internal jugular vein dimensions. *Acad Emerg Med* 2010; 17: 100–102.
81. Sundstrøm T, Asbjørnsen H, Habiba S, et al. Prehospital use of cervical collars in trauma patients: a critical review. *J Neurotrauma* 2014; 31: 531–540.
82. Nakajo M, Onohara S, Shinmura K, et al. Computed tomography and magnetic resonance imaging findings of brain damage by hanging. *J Comput Assist Tomogr* 2003; 27: 896–900.

83. Graus FF and Slatkin NEN. Papilledema in the metastatic jugular foramen syndrome. *Arch Neurol* 1983; 40: 816–818.
84. Al-Hilali N, Nampoory MR, Ninan VT, et al. The superior vena cava syndrome: late presentation after hemodialysis catheter removal. *Saudi J Kidney Dis Transpl* 2003; 14: 186–189.
85. Alperin N, Roach RC, Lee SH, et al. Evidence for the importance of extracranial venous flow in patients with idiopathic intracranial hypertension (IIH). *Acta Neurochir Suppl* 2004; 95: 129–132.
86. Yang Z-J, Zhang X-Y, Shen J-F, et al. [The impact of positive end-expiratory pressure on cerebral perfusion pressure and hemodynamics in patients receiving lung recruitment maneuver]. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue* 2008; 20: 588–591.
87. Pulitanò S, Mancino A, Pietrini D, et al. Effects of positive end expiratory pressure (PEEP) on intracranial and cerebral perfusion pressure in pediatric neurosurgical patients. *J Neurosurg Anesthesiol* 2013; 25: 330–334.
88. Kiehna EN, Huffmyer JL, Thiele RH, et al. Use of the intrathoracic pressure regulator to lower intracranial pressure in patients with altered intracranial elastance: a pilot study. *J Neurosurg* 2013; 119: 756–759.
89. Citerio G, Vascotto E, Villa F, et al. Induced abdominal compartment syndrome increases intracranial pressure in neurotrauma patients: a prospective study. *Crit Care Med* 2001; 29: 1466–1471.
90. Scalea TM, Bochicchio GV, Habashi N, et al. Increased intra-abdominal, intrathoracic, and intracranial pressure after severe brain injury: multiple compartment syndrome. *J Trauma* 2007; 62: 647–656.
91. Guinet P, Joseph DK, Schneider SM, et al. Decompressive laparotomy to treat intractable intracranial hypertension after traumatic brain injury. *J Trauma* 2004; 57: 687–693; discussion: 693–695.
92. Sugerman HJ. Hypothesis: preeclampsia is a venous disease secondary to an increased intra-abdominal pressure. *Med Hypotheses* 2011; 77: 841–849.
93. Hendrickson S, Chacko L and Wilson MH. Raised intracranial pressure following abdominal closure in a polytrauma patient. *JRSM Open* 2015; 6: 2054270414565958.
94. Fogarty JA, Otto C, Kerstman E, et al. Visual Impairement Intracranial Pressure Summit Report. ston.jsc.nasa.gov. 2011, http://ston.jsc.nasa.gov/collections/trs/_techrep/TP-2011-216160.pdf (accessed 8 June 2014).
95. Bozeman WP and Idris AH. Intracranial pressure changes during rapid sequence intubation: a swine model. *J Trauma* 2005; 58: 278–283.
96. Willie CK, Macleod DB, Shaw AD, et al. Regional brain blood flow in man during acute changes in arterial blood gases. *J Physiol* 2012; 590: 3261–3275.
97. Wilson MH, Edsell MEG, Davagnanam I, et al. Cerebral artery dilatation maintains cerebral oxygenation at extreme altitude and in acute hypoxia – an ultrasound and MRI study. *J Cereb Blood Flow Metab* 2011; 31: 2019–2029.
98. Wilson MH, Davagnanam I, Holland G, et al. Cerebral venous system and anatomical predisposition to high-altitude headache. *Ann Neurol* 2013; 73: 381–389.
99. Sagoo RS, Hutchinson CE, Wright A, et al. Magnetic resonance investigation into the mechanisms involved in the development of high-altitude cerebral edema. *J Cereb Blood Flow Metab*. Epub ahead of print 8 January 2016. DOI: 10.1177/0271678X15625350.
100. Zamboni P, Menegatti E, Weinstock-Guttman B, et al. The severity of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis is related to altered cerebrospinal fluid dynamics. *Funct Neurol* 2009; 24: 133–138.
101. Bateman GA. The pathophysiology of idiopathic normal pressure hydrocephalus: cerebral ischemia or altered venous hemodynamics? *AJNR Am J Neuroradiol* 2008; 29: 198–203.
102. Chung C-P, Wang P-N, Wu Y-H, et al. More severe white matter changes in the elderly with jugular venous reflux. *Ann Neurol* 2011; 69: 553–559.
103. Rohr A, Mórocz IA, Chung C-PC, et al. Pathogenesis of leukoaraiosis: Role of jugular venous reflux. *MedHypotheses* 2010; 75: 6–6.
104. Zivadinov RR, Poloni GUG, Marr KK, et al. Decreased brain venous vasculature visibility on susceptibility-weighted imaging venography in patients with multiple sclerosis is related to chronic cerebrospinal venous insufficiency. *BMC Neurol* 2011; 11: 128–128.
105. Louveau A, Smirnov I, Keyes TJ, et al. Structural and functional features of central nervous system lymphatic vessels. *Nature* 2015; 523: 337–341.